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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,093	09/29/1999	KAZUHIRO OHSUYE	001560-373	5533

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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1652	27

DATE MAILED: 09/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/402,093	OHSUYE ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-11,13,14,16-23 and 25-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6-11, 13, 14, 16-23, 25-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *23* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 22, 2003 has been entered.

The AF amendment filed December 26, 2002 amending the specification to correct clerical issues, canceling claims 2-5, 12 and 15 and adding claims 29-49 has been entered.

Claims 1, 6-11, 13, 14, 16-23 and 25-49 are pending.

Specification

The instant disclosure contains sequence disclosure that is encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. 37 CFR 1.821(d) requires the use of assigned sequence

identifier in all instances where the description or claims of a patent application discuss sequences.

For example, sequences such as RHHGP[G] (if they are sequences and not abbreviations) are recited without sequence identifiers (pages 31 and 34). Furthermore, the sequences should not contain amino acids in brackets.

Further, the Sequence Listing filed June 7, 2002 is objected because of the following. SEQ ID NO:25 is given as "Arg His His Gly Pro Xaa", where Xaa=Gly. Thus, SEQ ID NO:25 should be given as "Arg His His Gly Pro Gly". Furthermore, it is described as "amino acid sequence containing a site cleaved by Kex2 Protease". The same description has SEQ ID NO:8 that is Ser Asp His Lys Arg.

Appropriate correction is required.

By the amendment filed December 26, 2002, different sequences and what, in some cases, appears to be abbreviations were designated as SEQ ID NO:25. For example, SEQ ID NO:25 is assigned to both RHHGP[G] and RHHGP-1 wherein both appear to be the abbreviations not sequences (page 8, 23, 24, 30 and 33).

35 U.S.C. 112, first paragraph, requires the specification to be written in "full, clear, concise, and exact terms." The specification is replete with terms which are not clear, concise and exact. The specification should be revised carefully in order to comply with 35 U.S.C. 112, first paragraph. Examples of some unclear, inexact or

verbose terms used in the specification are: throughout the specification the terms "RHHGP[G]" and "RHHGP-1" while assigned SEQ ID NO:25 appear to be abbreviations, *supra*. For example, the specification recites "a fusion protein ... referred to hereinafter as RHHGP[G]" (e.g., page 21, lines 5-13); "amidated GLP-1(7-36)NH_2 (referred to hereinafter as RHHGP-1) [SEQ ID NO:25] (page 23). Further, the specification refers to "Purification of RHHGP[G]" and "purity of RHHGP[G]" (page 31, lines 21 and 35, respectively). Further, the specification recites, for example, "Excision and purification of GLP-1 (7-37) from RHHGP[G]" (page 32, lines 10-11); "RHHGP[G] obtained in Example 4 was converted to RHHGP-1 using an amidation enzyme" (page 33, lines 26-27), etc.

The use of brackets in" [SEQ ID NO:25]" introduced by the amendment (instead of parentheses) is confusing because brackets may indicate the deleted terms.

In conclusion, the specification is written in a way which precludes a complete and clear understanding of the invention and therefore its full and diligent examination.

At least the following objections and rejections are deemed to be necessary.

Claim Objections

Claims 14, 16, 17, 22 and 38-40 are objected to because of the following informalities:

Claims 14, 16, 17, 22 and 38-40 recite the method "GLP-1". It is suggested that the first time an abbreviation is used in the claims, that the abbreviated term be written out in full, followed by its abbreviation in parenthesis.

Claims 21 is objected to because of the following informalities: "and/or a salt" is missing space between "and/or" and "a salt" on line 2.

Appropriate correction is required.

Applicant is advised that should claims 6-9 be found allowable, claims (18 and 41), (19 and 42), (20 and 43), and (21 and 44), respectively, will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6-11, 13, 14, 16-23 and 25-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 6-11, 13, 14, 16-23 and 25-28 are directed to a process of making a peptide using a cell transformed with a DNA encoding a fusion protein comprising a peptide of interest and a helper peptide, a DNA encoding said fusion protein and a vector and a cell comprising thereof. New claims 29-49 are drawn to a process of making a peptide using a cell transformed with a DNA encoding a fusion protein comprising a peptide of interest and a helper peptide, wherein a protective peptide is added to a peptide of interest, and a vector and a cell comprising a DNA encoding said fusion protein.

Claims 1, 6-11, 13, 18-21, 23, 25-37 and 41-49 do not limit a peptide of interest by either structure or function. Therefore, the claims recite a genus of peptides of interest, a genus of helper peptides and a genus of protective peptides. These genera encompass an infinite number of peptides of any structure and from any source both naturally occurring and man made as long as the isoelectric point of the fusion protein is between 8-12. Claims 14, 16, 17, 22 and 38-40 are directed to a peptide of interest, GLP-1 derivative.

The specification does not contain any disclosure of the structure of GLP-1 peptide and of the structure and function of all GLP-1 derivatives. The genus of DNAs that comprise the DNA molecules encoding thereof is a large variable genus with the potentiality of encoding many different proteins. Therefore, many structurally and functionally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. The specification discloses only a three species of the claimed genus of fusion proteins comprising GLP-1 (Figures 11-13). The specification does not disclose the isoelectric points of said fusion proteins. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the "functionality" of encoding a GLP-1 derivative and fails to provide any structure: function correlation present in all members of the claimed genus. The specification does not teach the production of any other peptide of interest. Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 1, 6-11, 13, 14, 16-23 and 25-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of making GLP-1 using fusion proteins shown at Figures 11-13, does not reasonably provide

enablement for a process of making of any peptide or GLP-1 using other fusion proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or the invention commensurate in scope with these claims.

Claims 1, 6-11, 13, 14, 16-23 and 25-49 are directed to a method for producing a highly purified peptide. Therefore, they are drawn to a method of making of a genus of a polypeptide of an unknown function and having any characteristics as long as the isoelectric point of the fusion protein is between 8 and 12. While the specification teaches a method of making of a highly purified GLP-1, it does not provide any guidance as to a process for producing a highly purified peptide of any function and characteristics. The specification does not disclose the isoelectric points of fusion proteins comprising GLP-1. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The claimed method encompasses purification of any peptide using a fusion of a peptide of interest and a helper peptide wherein the attachment of a helper peptide would change characteristics of the peptide of interest. This would involve experimentation to find the peptide that being attached to the peptide of interest would change characteristics of the latter, so that it would become possible to use this characteristics in various purification techniques.

The state of the art is such that it is unpredictable which helper should be used for each peptide of interest, to enable the claimed method for any peptide of interest, and the specification provides no guidance on the matter.

It is known in the art that the relationship between the sequence of a polypeptide and its properties and tertiary structure is neither well understood nor predictable. The specification does not how to separate any peptide of interest from any helper when there is no proteolytic cleavage connecting said peptides.

Consequently, excessive trial and error experimentation would be required to identify the necessary helper sequence that would impart the properties allowing the production of a highly purified peptide of interest since the amino acid sequence of such a helper peptide useful with any peptide of interest could not be predicted *a priori*. The specification provides no guidance on predicting a helper of what structure would be suitable for a given peptide of interest. Furthermore, the development of an appropriate purification scheme for a peptide with known characteristics requires additional trial and error experimentation.

Therefore, one skilled in the art would require guidance as to how to make a highly purified peptide of any function and structure by a claimed process. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 6-11, 13, 14, 16-23 and 25-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 6-11, 13, 14, 16-23 and 25-49 are as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. The omitted elements are: the proteolytic cleavage site between a peptide and interest and a helper peptide and a protective peptide.

Claims 1 and 29 recite "cleaving off from the peptide of interest that has the helper peptide added thereto obtained in step (...), the helper peptide and the peptide of interest" where it appears cleaving off the peptiode of interest from the helper peptide is intended (emphasis added). Claim 29(2) is confusing on the whole and specifically as reciting "the peptide of interest that has the helper peptide added thereto as desired" while claim 29(1) requires a fusion protein comprising the peptide of interest that has a the helper peptide added thereto (emphasis added).

Claim 9 recites the limitation "steps (1) to (5)" in line 3. There is insufficient antecedent basis for this limitation in the claim. Claim 1 from which claim 9 depends has 3 steps. Similarly claim 34.

Claim 23 is confusing as reciting "wherein endotoxin is present in the peptide of interest" (emphasis added). Nothing can be "present" in the peptide of interest. Peptide of interest is a peptide. Endotoxin can not be present in another peptide but only in a mixture of peptides or in a peptide preparation. Furthermore, there is insufficient antecedent basis for "endotoxin" in the claim. Claim 23 depends from claim 1 that does not recite endotoxin. Similarly claim 46. Furthermore, Claim 46 is unclear because claim 29, from which it depends, refers to the purification of "a peptide having a desired biological activity", i.e, "peptide of interest" not to "the final purified product" comprising endotoxin.

Claims 28 and 47 recite "a modification reaction". The type and number of said reactions is indefinite rendering the metes and bounds of the claims unascertainable.

Claims not specifically rejected herein are rejected as dependent from the rejected base claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> a person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6-11, 13, 18-23, 25-27 and 41-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Tarnowski et al.

Tarnowski et al. (US Patent 5,202,239, form PTO-1449 filed March 8, 2000) teach a method for producing a peptide by expressing a peptide as fusion protein having a high pI (of about 8 or greater), separating the fusion proteins from all other host cell proteins, and separation of the carrier from the peptide after cleavage (abstract, column 1, lines 40-58, claims 1-8).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) a patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14,16,17 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tarnowski et al. in view of Bell et al.

The teachings of Tarnowski et al. are outlined above.

Bell et al. (form PTO-892 mailed October 10, 2001) teach GLP-1 and its physiological importance.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the method taught by Tarnowski et al. to the expression of GLP-1.

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tarnowski et al. in view of Mojsov et al.

The teachings of Tarnowski et al. are outlined above.

Mojsov et al. (form PTO-892 mailed June 25, 2002) teach a natural derivative of GLP-1(7-37), GLP-1 (7-36)NH_2, and its physiological importance.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the method taught by Tarnowski et al. to the production of a highly purified GLP-1 and than to make an amidated form thereof, physiological importance of which is taught by Mojsov et al.

Response to Arguments

With regard to the 112, 1st paragraph, written description rejection Applicants argue that "the assertion that the claims encompass a genus comprising a peptide of not limited by structure is thus correct" (Remarks filed April 10, 2002, page 4, 1st full paragraph). Applicants continue "the fact that not all peptides of interest which could be used in the claimed method does not mean that the written description has not been

met. ... GLP-1 is given as an example of a peptide of interest" (ibid, page 5, 1st full paragraph). This is not persuasive because a method of use of a product (a fusion protein with the isoelectric point 8-12) is not described if said product is not described. The written description of a chemical compound is highly insufficient when represented by a single characteristic. The list of peptides on page 10 does not obviate said deficiency because the fusion protein comprising any of said peptides and having pI 8-12 that would allow the successful purification of a peptide is not described. With regard to GLP-1 and derivatives thereof, Applicants argue that "such peptides are well known in the art" (ibid, page 6). This is not persuasive because as an essential material the structure of GLP-1 must be described in the specification.

Applicant's arguments filed December 26, 2002 have been fully considered but they are not persuasive.

With regard to the 112, 1st paragraph, enablement rejection Applicants argue that "the particular structure, function and characteristics of the peptide of interest and structure of the helper peptide are not critical to the claimed process and need not be specified in the claims. The peptide of interest is expressed as an intermediate peptide comprising the peptide of interest and a helper peptide which a added to the peptide of interest. In this intermediate peptide (or precursor peptide) the helper peptide changes the physicochemical properties, i.e., isoelectric point, of the peptide of interest so that

the intermediate (or precursor) peptide can be easily, and stably purified. After purification of the intermediate peptide, the intermediate peptide is cleaved to liberate the peptide of interest. This method does not depend upon the particular structure, function or characteristics of a particular peptide of interest or the structure of the helper peptide, but instead can be generally used by those skilled I the art for any peptide of interest" (paragraph bridging pages 15-16). This is not persuasive because the specification does not provide an evidence that the only characteristic of a molecule that is important for its purification is the isoelectric point. In fact, the state of the art teaches that the purification of peptides depends on many properties and is, in most cases, an empirical process. Furthermore, the claims do not include the purification of an "intermediate peptide" that comprises peptide of interest and a helper peptide as described by Applicants in the recited paragraph.

With regard to the 102(b) rejection applicants argue that "the molecular weight of a peptide having 50 amino acids is about 6kD. By contrast, the carrier protein of Tarnowski et al has a molecular weight about 10 to 50 kD. Nor does Tarnowski et al disclose or suggest a helper peptide which will provide an isoelectric point of the combined peptide of interest and helper peptide of between 8-12 " (page 17). This is not persuasive because, depending on the sequence, a peptide containing 50 amino acids can have a molecular weight of 10 kD. For example, a high content of tryptophan

would result in that. Furthermore, Tarnowski et al tech an isoelectric point of about 8 or greater that includes 8-12 and, in fact, implicitly means the range of pI 8-12.

With regard to the 103(a) rejection, Applicants argue that Mojsov et al. "suggests nothing of the problem of producing such a protein recombinantly, e.g., solubility problems, and hoe to overcome it, e.g., by using a helper to alter the isoelectric point of the peptide of interest" (page 19). As a secondary reference in the 103(a) rejection, the Mojsov et al. reference does not have to disclose the same invention but only to make it obvious. While Mojsov et al. do not teach the instant invention in its entirety, they teach GLP-1 and provide the motivation to produce it in high quantities, i.e. recombinantly.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

September 26, 2003